

ANALYSIS OF PHARMACEUTICAL/POLYMER SOLID DISPERSIONS  
PRODUCED BY SUPERCRITICAL CARBON DIOXIDE-ASSISTED TECHNIQUES

A Thesis

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**Abstract:**

In the pharmaceutical industry, the production of solid dispersions is generally accepted as a method to enhance the oral bioavailability of drugs with low aqueous solubility. Two processes commonly employed to create solid dispersions are examined in this research. The first technique dissolves the drug and carrier in a common organic solvent and is followed by a solvent-removal operation. The second method processes both the drug and polymer in a high-pressure mixer with supercritical carbon dioxide. This method is intended to simulate the temperature and pressure conditions of carbon dioxide-assisted hot-melt extrusion.

Organic solvent-based solid dispersion formulation techniques are accompanied by environmental challenges, due to disposal of the solvent, and are generally more costly than extrusion applications. However, the application of hot-melt extrusion technologies has been limited due to the temperature-sensitive nature of the drugs and the high processing temperatures associated with the extrusion process. The inclusion of supercritical fluids, such as carbon dioxide, in the polymer-melt extrusion method has proved to significantly lower processing temperatures, thereby extending the technique to thermo-labile compounds.

Yet the properties of solid dispersions created in this manner have traditionally been unpredictable. This study systematically analyzes the properties of solid dispersions formulated by supercritical carbon dioxide-assisted techniques and compares these characteristics to those of solid dispersions created using the organic-solvent method.

Composite samples of 4-aminosalicylic acid, a sample drug compound, and eudragit E100, an acrylate block copolymer, were formulated using both the organic

solvent method and a carbon dioxide-assisted high-pressure mixing process. Due to the costly nature of the drug and polymer, the high-pressure mixer approach was employed to simulate extruder conditions in a batch operation and characterize the suitability of materials for extrusion. Drug-polymer composites were made using the organic-solvent method. The processing temperature of these samples was kept low so that it could be used as a standard to examine the effects of heat. In the high-pressure mixer technique, the same ratio of drug-polymer was processed with supercritical carbon dioxide. Process temperatures and carbon dioxide pressures were varied.

Samples from each method were analyzed using differential scanning calorimetry (DSC) to measure thermal properties and Fourier-transform infrared (FTIR) spectroscopy to examine drug-polymer interactions and dispersion properties. High-pressure differential scanning calorimetry (HPDSC) was further utilized to examine the morphology of the composites while in equilibrium with carbon dioxide. Results of this study examine the use of a high-pressure mixer to simulate extrusion conditions and distinguish between composites made by organic solvent and supercritical carbon dioxide-assisted processes.

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## **I. INTRODUCTION**

### **1.1 Pharmaceutical Composite Formulation Techniques**

Pharmaceutical composites are generally comprised of active drug compounds and biodegradable polymer carriers. The inclusion of polymer carriers is essential to control both the rate of drug delivery and the formation of solid dispersions. The production of solid dispersions is commonly acknowledged as a method to enhance the aqueous solubility, thereby increasing the oral bioavailability, of drugs with low solubility in water. The production methods used to create dispersions can generally be divided into two categories.

The first technique dissolves the drug and carrier in a common organic solvent and is followed by a solvent-removal operation, such as evaporation. This evaporation can be accomplished, for example, by spray-drying, wherein the solution is dispersed into fine droplets. By increasing the surface area of the solution, the solvent is rapidly evaporated, and the resulting composite particles are collected. The second method melts both the carrier and drug, and then cools the melt to form a solid dispersion. In fact, some methods allow for the distribution of the solid drug in a molten carrier to minimize processing temperatures and reduce drug degradation. In recent years, hot-melt extrusion has become an attractive alternative to traditional solvent-based methods (Breitenbach, 2002). Extrusion offers a solvent-free process to produce solid dispersions. In addition to concerns regarding residual solvent, solvent-based solid dispersion formulation techniques are accompanied by environmental challenges due to disposal of the organic solvent and are generally more costly than extrusion applications; therefore, it seems that the extrusion technique is preferable (Forster, 2001).



## 1.2 Expanding the Applicability of Extrusion in Pharmaceutical Applications

Although melt-extrusion methods can be applied to disperse drugs in a polymeric matrix down to the molecular level (Breitenbach, 2002), the number of extrusion-based solid dispersion applications in the pharmaceutical industry is limited. The long residence time and high temperature needed for processing leads to drug degradation; therefore, the technology has only been applied to polymers that exhibit low glass transition temperatures ( $T_g$ ). The applicability of a material for the extrusion process is dictated by its  $T_g$ , which is the transition between regions of high and low molecular mobility, and the sensitivity of the polymeric matrix or drug toward heat and shear force.

For thermo-labile compounds, a plasticizer may be added to the composite. The small molecules traditionally used as plasticizers increase polymer chain mobility by weakening the polymer-polymer interactions, thus reducing viscosity and  $T_g$ , and lowering minimum process temperatures (Verreck, 2003). However, this added material increases the final weight of the product, which is a distinct disadvantage in pharmaceutical applications. Research has shown that drug compounds can act as plasticizers when processed with polymers. For example, the common drug compound ibuprofen has proved to function as a non-traditional plasticizer in hot-melt extrusion applications. Composites of 60/40 wt % ibuprofen/ethyl cellulose have been extruded at temperatures as low as 60°C, although the  $T_g$  of ethyl cellulose exceeds 130°C (DeBranbender, 2002).

Supercritical fluids (SCFs) are at such temperature and pressure conditions that they exhibit gas-like transport properties but also demonstrate liquid-like solvent capacities and densities. Consequently, an SCF can act as a temporary plasticizer for the

polymeric carrier and as a solvent for the drug compound, thereby assisting in the formation of solid dispersions. Moreover, when the material exits the extruder and the pressure is released, the SCF expands to its gaseous form and escapes from the polymer to create a foam. This foam contains no plasticizer or solvent residue and is easily milled into powder for feeding into a pill press, thereby reducing the thermal and mechanical stress on the product relative to conventional solvent-based methods. Thus, the application of SCFs to assist the extrusion process has expanded the technique to thermolabile compounds.

### **1.3 Supercritical Carbon Dioxide**

Supercritical carbon dioxide (SC-CO<sub>2</sub>) is commonly used in SCF applications because of its relatively low critical temperature ( $T_c = 31.05^\circ\text{C}$ ). Additionally, carbon dioxide is non-flammable, inert, inexpensive, environmentally benign relative to other solvents, and exhibits antibacterial properties. Furthermore, the compound is not yet regulated by the Food and Drug Administration, making it particularly suitable for pharmaceutical use.

While this area of research remains somewhat novel, new methods to create and characterize polymer-drug composites using SCF-assisted extrusion are of particular interest to pharmaceutical research groups. Previous research in the laboratory of Dr. David Tomasko studied the viscosity reduction and glass-transition temperature depression of various pharmaceutical polymers under SC-CO<sub>2</sub>. For example, DSC trials conducted by Hongbo Li examine the contrasting effects of pressurized nitrogen and carbon dioxide in equilibrium with polystyrene. Over a pressure range of 1 to 65 bar,

carbon dioxide decreases the glass-transition temperature 15 times as much as nitrogen. At 65 bar, the  $T_g$  of polystyrene is approximately 40°C below the  $T_g$  at ambient pressure. In addition, polymer-drug composites have been processed using traditional and tandem carbon dioxide-assisted extrusion processes, and the results have been characterized using DSC and fluorescence microscopy.

This research has been performed in conjunction with the Janssen Research Foundation in Belgium. There, researchers have used carbon dioxide-assisted extrusion to study dissolution rates and morphological effects of carbon dioxide on drug-polymer composites. Thermogravimetric analysis (TGA) has been utilized to determine upper process temperature limits for various polymers and drug compounds, and high pressure liquid chromatography (HPLC) has been used to examine drug degradation.

In spite of the simplicity of extrusion as a manufacturing method to create solid dispersions, the number of marketed products arising from this approach has been disappointing (Craig, 2002). The lack of predictability of solid-dispersion behavior can be attributed to a poor understanding of its properties. In solid dispersions, the physical state of the drug is often changed from crystalline to amorphous. The absence of the crystalline lattice leads to dramatically improved dissolution properties, which is beneficial for drugs with low solubility (Six, 2002). However, in the majority of cases, it is unclear whether the drug is present as a molecular, a crystalline particulate, or an amorphous particulate dispersion (Craig, 2002). Finding a method to systematically examine the properties of solid dispersions produced by SC-CO<sub>2</sub> assisted extrusion, and the effects of SC-CO<sub>2</sub> and drug concentration on these properties, is crucial for the application of this technology in the pharmaceutical industry.

## 1.4 Purpose

The aim of this research was to characterize the physical properties of solid dispersions resulting from SC-CO<sub>2</sub>-assisted mixing techniques, and to differentiate these products from those created using standard organic-solvent methods. Significant considerations included the verification of sufficient drug dispersion within the polymer carrier and the prevention of drug degradation. The primary objective was to obtain representative samples from both the organic-solvent and SC-CO<sub>2</sub>-assisted melt formulation techniques, the latter while varying system parameters. Resulting samples were then characterized using DSC and FT-IR spectroscopy. Information on composite samples was collected using a batch SC-CO<sub>2</sub>-assisted melt operation with the goal of determining the suitability of a material for melt extrusion. The results of this research should help to provide fundamentals for the widespread application of extrusion technology in the pharmaceutical industry.

## II. EXPERIMENTAL

### 2.1 Materials

The materials used in the composite formulations consisted of a model drug compound and a model pharmaceutical polymer. Due to the costly nature of authentic drug compounds and pharmaceutical polymers, model materials were utilized in this research. The model drug compound, 4-aminosalicylic acid (4-ASA), is a specific bacteriostatic agent applied in the treatment of pulmonary tuberculosis (Verreck, 2005). The 4-ASA (99% purity, Batch #11111TB) was supplied by Aldrich<sup>®</sup>. The drug, a thermally-labile active substance, melts at 135°C with significant decomposition occurring near 120°C (Verreck, 2005). The chemical structure of 4-ASA is shown below in Figure 1.

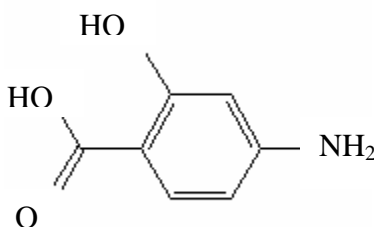


Figure 1: Chemical Structure of 4-aminosalicylic acid

The model pharmaceutical polymer, Eudragit E100, is an acrylate block copolymer composed of 2-dimethyl aminoethyl methacrylate, methyl methacrylate, and n-butyl methacrylate in a molecular ratio of 2:1:1, respectively. Eudragit E100 (Lot #8320401074) was obtained from Rhom Pharma Polymers<sup>®</sup> in the form of 3 mm diameter pellets. The model pharmaceutical polymer experiences a glass transition in the temperature region of 50°C. Significant thermal decomposition of the polymer occurs at temperatures greater than 200°C. Eudragit E100 is soluble in acidic solutions (pH < 5)

and numerous organic solvents such as isopropanol, ethanol, and acetone. The chemical structure of Eudragit E100 is depicted in Figure 2.

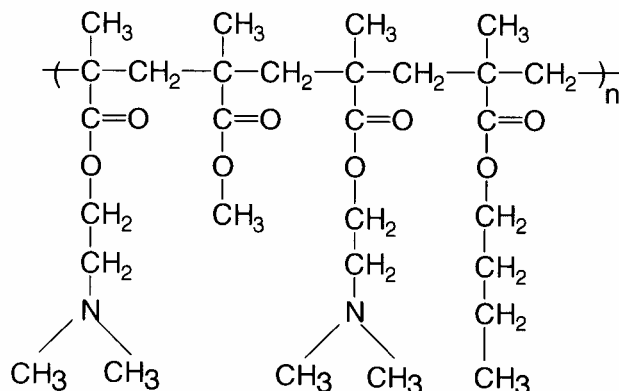


Figure 2: Chemical Structure of Eudragit E100

The carbon dioxide used in both the CO<sub>2</sub>-assisted high-pressure mixing technique, as well as the high-pressure DSC analyses, was 3.0 grade (> 99.9% purity) supplied by Praxair. Acetone, used as the solvent in the organic solvent formulation method, was obtained from Mallinckrodt Chemicals (> 99.7% purity, Lot #A46B34).

## 2.2 Organic Solvent Method

In the organic-solvent formulation method, a 10 wt% 4-ASA in Eudragit E100 solution was made. Based on mutual solubility of the drug and polymer, as well as its high volatility, acetone was chosen as the solvent. A minimal amount of acetone was employed such that the drug and carrier were completely dissolved after sufficient agitation. The solvent was then evaporated using a Fisher Isotemp Vacuum Oven, Model 282. The vacuum oven temperature was set at 35°C, which is below the T<sub>g</sub> of Eudragit E100 and well under the decomposition temperatures of both the drug and polymer. By

maintaining low temperatures throughout the formulation of these composites, it was assumed that the resulting samples could serve as standards against which the effects of heat could be compared. The pressure in the oven was decreased to approximately 0.1 in. of Hg using a Welch Duo-seal Vacuum Pump with a 1 horsepower motor manufactured by Franklin Electric. The organic-solvent method composites were held under these conditions for a period of two days. The samples were then ground with a mortar and pestle, and one of the two composites created in this manner was again placed in the vacuum oven under the aforementioned conditions to ensure adequate solvent removal.

### **2.3 SC-CO<sub>2</sub>-Assisted High-Pressure Mixing Method**

The high-pressure mixing method was used to simulate the temperature and pressure conditions in CO<sub>2</sub>-assisted hot-melt extrusion applications. These batch operations used dramatically less material than a continuous extrusion process while creating a qualitatively similar foam product.

In the high-pressure mixer technique, the same ratio of drug:polymer (10:90 wt%) was melted in a Pressure Products Industries, Inc. FC Series Reaction Vessel (rated 6000psi at 650°F). A calibration curve for the temperature inside the reaction vessel was constructed prior to composite formulation. The mixture of drug and polymer was heated for two hours at the desired process temperature, which was varied from 80-120°C. Carbon dioxide was then added to the reaction vessel via an ISCO Model 500D Syringe Pump. Control of the pressure was established using an ISCO Series D Pump controller. The reaction vessel was given sufficient time to equilibrate with carbon dioxide at the desired pressure, either 1500 or 2000psi. Therefore, once the carbon dioxide reached the

reaction vessel, the compound was in its supercritical state. The Dynamag Magnetic Drive mixing rotor was then set to 250 rpm using a SP500 Rotor Control and activated, and the sample was processed at the set conditions for four hours. Afterward, the reaction vessel was given time to cool, the pressure was released, and the resulting samples were crushed using a mortar and pestle. A photograph of the SC-CO<sub>2</sub>-assisted high-pressure mixing apparatus is shown in Figure 3.



Figure 3: Photograph of high-pressure mixing apparatus (mixer left, syringe pump right)

Initially, samples processed at the upper temperature ranges became significantly discolored. A high-pressure mixer sample containing only polymer was then processed at 120°C and 1500psi. Because no discoloration was observed in the pure polymer sample, it was confirmed that the discoloration was attributed to drug degradation caused by oxidation during the melting step. Therefore, a carbon-dioxide purging step prior to heating was employed in the processing of subsequent samples.



## 2.4 Differential Scanning Calorimetry

Representative composite samples were obtained for each set of system parameters. Differential Scanning Calorimetry was performed to evaluate the thermal properties of the pure drug and polymer, as well as the characteristics of both the organic-solvent and high-pressure mixer composite samples. Eudragit E100 is an amorphous copolymer and thus possesses a glass transition. DSC analyses plot the heat flow as a function of temperature. If the composite sample is in an amorphous state, it will undergo a glass transition corresponding to a decrease in heat capacity. A downward shift will be observed in the plot, and this endothermic transition is used to determine the composite's  $T_g$ . Frequently, the glass transition is accompanied by an enthalpy relaxation, which is seen as an endothermic signal superimposed on the glass transition. In its pure state, 4-ASA is a crystalline drug and thus exhibits a melting peak. If the drug is present in its crystalline form, an inverse peak in the plot corresponding to the melting point of the crystals will be observed. Figure 4 presents a generic DSC plot with common features. The effects of processing temperatures and  $\text{CO}_2$  pressures on  $T_g$  depression and dispersion characterization are studied.

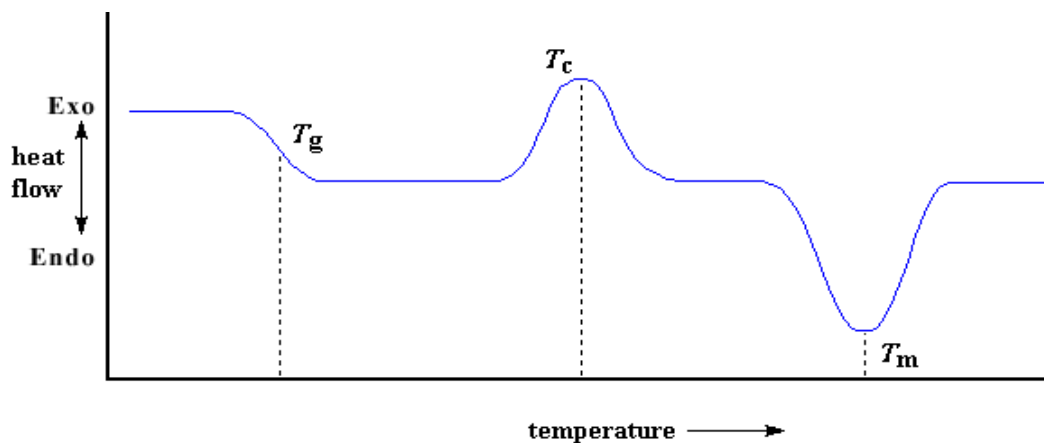


Figure 4: Sample DSC Scan (State of composite will dictate observed trends)

The analyses were performed using a TA Instruments DSC 2920 Differential Scanning Calorimeter. Nitrogen was used as a purge gas at a rate of 50 mL/min. The DSC cell was calibrated using indium as a reference material. The samples were analyzed in hermetically sealed TA Instruments pans. Approximately 10 mg of sample was heated from 25°C to 190°C, which encompassed the entire range of the glass-transition and melting peaks, with a heating rate of 10°C/min. The glass-transition temperature was determined at the inflection point as half the height of the shift in the heat-flow signal. The melting temperature was measured by determining the minimum point of the inverse peak, and the enthalpy of melting was calculated by integrating the area of the inverse peak. The samples were analyzed at least in duplicate, depending on the precision of the results. Figure 5 is a photograph of the differential scanning calorimeter apparatus employed in this research.



Figure 5: Photograph of Differential Scanning Calorimeter

Additionally, samples were analyzed using high-pressure differential scanning calorimetry to determine the effects of carbon dioxide as a plasticizer on the composites.

A TA Instruments high-pressure DSC cell was added to the regular DSC setup, and pressurized carbon dioxide was injected using an ISCO Model 500D Syringe Pump.

## **2.5 Fourier Transform Infrared Spectroscopy**

Fourier-transform infrared (FTIR) spectroscopy was performed on each of the samples to determine the structure of the organic compounds and to identify the presence of specific functional groups within a sample. Furthermore, drug-polymer interactions were examined using the resulting spectra. In this case, the infrared spectra were obtained using a scale of wave numbers ( $\text{cm}^{-1}$ ). The benefit to using wave numbers is that the units are directly proportional to energy, so the higher the wave number, the higher the energy of the infrared radiation.

Spectra are obtained by passing infrared radiation through a sample and determining what fraction of incident radiation is absorbed at a particular energy. The energy of a peak in the spectrum corresponds to the frequency of vibration of part of the sample compound. For a molecule to have IR absorptions, an electric dipole moment of the molecule must change, which corresponds to an excitation of a vibrational energy state of a functional group. A single molecule can have many distinct vibrational states.

The analyses were performed using a Thermo Nicolet Nexus 470 FTIR ESP. 3-5 mg of composite sample was added to approximately 100 mg of KBr (s). The mixture was then ground to a fine powder using a mortar and pestle, and transparent discs were formed using a pellet press. The discs were then placed in the FTIR spectroscopy apparatus, and spectra were collected. The range of the collected spectra was 4000-400  $\text{cm}^{-1}$ . Figure 6 is a photograph of the FTIR spectroscopy apparatus used in this research.



Figure 6: Photograph of Fourier-Transform Infrared Spectroscopy Apparatus

### III. RESULTS AND DISCUSSION

#### 3.1 Qualitative Results of Formulation Methods

Qualitatively, the product of the organic solvent method was a dark orange translucent solid of almost crystalline density and appearance. In contrast, the resultant sample from the high-pressure mixer was porous foam of a light brown shade, similar in color to a combination of the pure drug and polymer. Figure 7 illustrates the different appearances of the product resulting from each method.

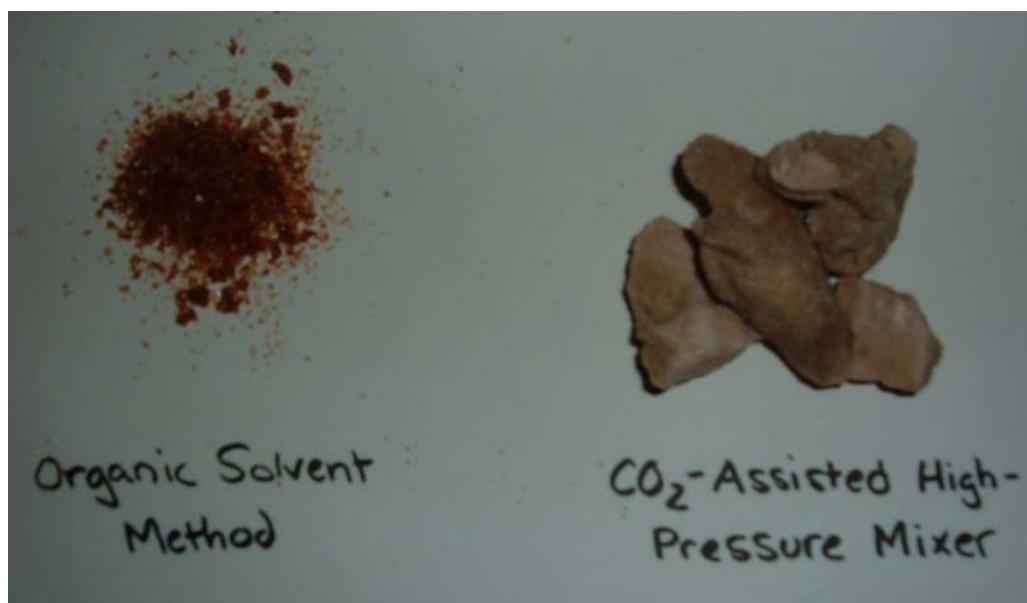


Figure 7: Photo of Organic Solvent and High Pressure Mixer (80°C, 1500psi) Products

Because the process temperatures during the organic solvent formulations were maintained well under the decomposition temperatures of both the drug and polymer, it was assumed that the resulting samples would serve as standards against which the effects of heat could be compared. However the discoloration of the sample indicates that product degradation may have occurred. The usage of acetone as a solvent may be responsible for this qualitative observation. It is assumed that the decomposition pathway for 4-ASA includes the “decarboxylation of the active ingredient with the

formation of carbon dioxide” (Verreck, 2005). This decarboxylation is generally caused by heat, but perhaps the electronegative oxygen of acetone triggers the drug’s decomposition.



Figure 8: Photo of Effect of Temperature on Appearance of Composite at 1500psi

As observed in Figure 8, this phenomenon of discoloration was also observed in the high-pressure mixing products. It seemed likely that the darkened color is due to degradation of the drug. To reinforce this conclusion, a sample was processed using pure Eudragit at 120°C and 1500psi. The color of the product is comparable to the samples formulated at the 80°C and 1500psi. Figure 9 confirms the prior suspicion that the discoloration of the composite product should be attributed to the degradation of the drug.



Figure 9: Comparison of Composite and Pure Polymer Processed in Mixer (120C, 1500 psi)

The discoloration was also observed when the pressure was increased from 1500 to 2000 psi. Whereas the composite processed at 80°C and 1500 psi looked much like pure Eudragit, the sample processed at 80°C and 2000 psi appears darker and more brittle (see Figure 10). It was therefore decided to add a carbon dioxide purging step, prior to heating, to minimize the drug degradation. In Figure 10, two samples are displayed for the 100°C, 2000 psi process conditions. The sample on the left was heated before the purging step, and the sample on the right was purged thoroughly with carbon dioxide before heating.



Figure 10: Composites Produced at Various Operating Conditions

Figure 11 depicts the effect of purging with carbon dioxide before heating more clearly. The product with the purging step appears very similar to the product of 80°C and 1500 psi, indicating minimum drug degradation.

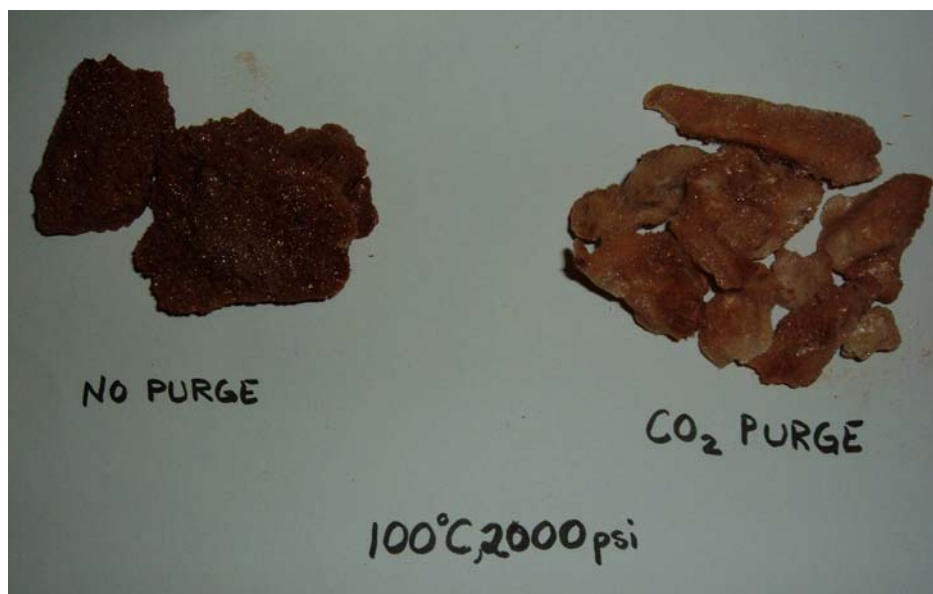


Figure 11: Composites produced with and without CO<sub>2</sub> purge



### 3.2 Differential Scanning Calorimetry Results

A summary of the DSC results is found in Table 1. Although, the OSM sample appears discolored, its drug enthalpy value is close to that of the pure drug and the composite processed at 80°C and 1500psi, indicating minimal degradation for both the OSM and the low parameter HPM samples. It is observed that the melting peak for the composite samples is approximately 20°C higher than for the pure drug. This could be the result of strong drug polymer interactions, namely hydrogen bonding, making the bonds of the solid material more difficult to break. It should be noted that the onset temperature for melting the composite is close to the pure drug melting temperature. Additionally, the byproducts of drug degradation, namely various aminophenols, have higher melting temperatures than the drug itself. It should also be noted that the melting peak for the OSM samples is noisier than that of the HPM samples, possibly indicating residual solvent. As the operating temperature for the HPM samples is increased, the drug enthalpy value is decreased, again confirming the suspicion of drug degradation. At 2000 psi, no melting peaks are observed for the drug. This could indicate complete degradation, but because no other byproduct signals are observed in the plot, it may also indicate that the drug is dispersed in its amorphous form. Only the HPM-100C-2000psi-C samples were purged with carbon dioxide prior to heating.

Table 1: Summary of DSC Results

	Polymer $T_g(^{\circ}\text{C})$	Drug $T_m(^{\circ}\text{C})$	Drug $\Delta H(\text{J/g})$
<b>Pure Compounds</b>			
Pure 4-aminosalicylic acid (1)	--	134.93	289.20
Pure Eudragit (1)	56.41	--	--
Pure Eudragit (2)	54.47	--	--
HPM-Eudragit-120C,1500psi (1)	56.24	--	--
HPM-Eudragit-120C,1500psi (2)	60.38	--	--
HPM-Eudragit-120C,1500psi (3)	60.06		

<b>Composites</b>		--	--
OSM-1 (1)	49.55	155.10	173.10
OSM-1 (2)	52.36	162.54	175.70
OSM-2 (1)	52.73	164.39	192.20
OSM-2 (2)	52.77	163.51	200.00
HPM-80C,1500psi (1)	55.04	152.57	181.70
HPM-80C,1500psi (2)	56.15	155.04	194.80
HPM-100C,1500psi (1)	43.87	152.23	63.53
HPM-100C,1500psi (2)	41.82	155.19	47.06
HPM-120C,1500psi (1)	44.70	150.75	43.35
HPM-120C,1500psi (2)	45.89	151.34	42.52
HPM-80C,2000psi (1)	52.97	--	--
HPM-80C,2000psi (2)	52.79	--	--
HPM-100C-2000psi-A (1)	48.41	--	--
HPM-100C-2000psi-A (2)	48.16	--	--
HPM-100C-2000psi-B (1)	52.09	--	--
HPM-100C-2000psi-B (2)	51.07	--	--
HPM-100C-2000psi-C (1)	55.44	--	--
HPM-100C-2000psi-C (2)	52.15	--	--
HPM-100C-2000psi-C (3)	55.25	--	--
HPM-100C-2000psi-C (4)	56.76	--	--

In Table 1, it is observed that the T<sub>g</sub> of the pelletized Eudragit is similar to the T<sub>g</sub> of HPM processed Eudragit, indicating that after the carbon dioxide is released, it no longer serves as a plasticizer. Figure 12 graphically depicts the glass transition temperatures of the HPM samples as a function of process temperature. It is observed that the T<sub>g</sub> of pure Eudragit is higher than the T<sub>g</sub> of composite samples confirming the plasticization effect of the drug 4-ASA.

The composite T<sub>g</sub> generally decreases as the process temperature is increased. At increased processing temperatures, viscosity is lowered, allowing for increased polymer chain mobility and better dispersion of drug. The higher the quality of drug dispersion, the more effectively the drug can act as a plasticizer. Drug degradation may have something to do with the slight increase in T<sub>g</sub> from 100°C to 120°C. Perhaps at 120°C, the degraded drug compound is not as effective of a plasticizer.

At 80°C, as pressure is increased from 1500 to 2000 psi, the Tg is lowered. Perhaps this can best be explained by the Free Volume Theory. As the carbon dioxide pressure is increased, more fluid dissolves in the polymer melt, which increases the space between molecules. Even after the pressure is released, this increased free volume reduces polymer chain interaction and therefore reduces Tg. However, at 100°C, the opposite phenomenon is observed. The Tg increases as processing pressure increases. Additionally, after the carbon dioxide purging step is included in this process, the Tg increases further, reaching values near that of the pure polymer. This phenomenon is difficult to explain, but it should be noted that the drug is in its amorphous form at 2000 psi. The hydroxyl group on 4-ASA can serve as a hydrogen bond donor, while the double bonded oxygen in Eudragit can serve as a hydrogen bond acceptor. As an amorphous dispersion is achieved, perhaps hydrogen-bonding between the drug and polymer can be used to explain this trend.

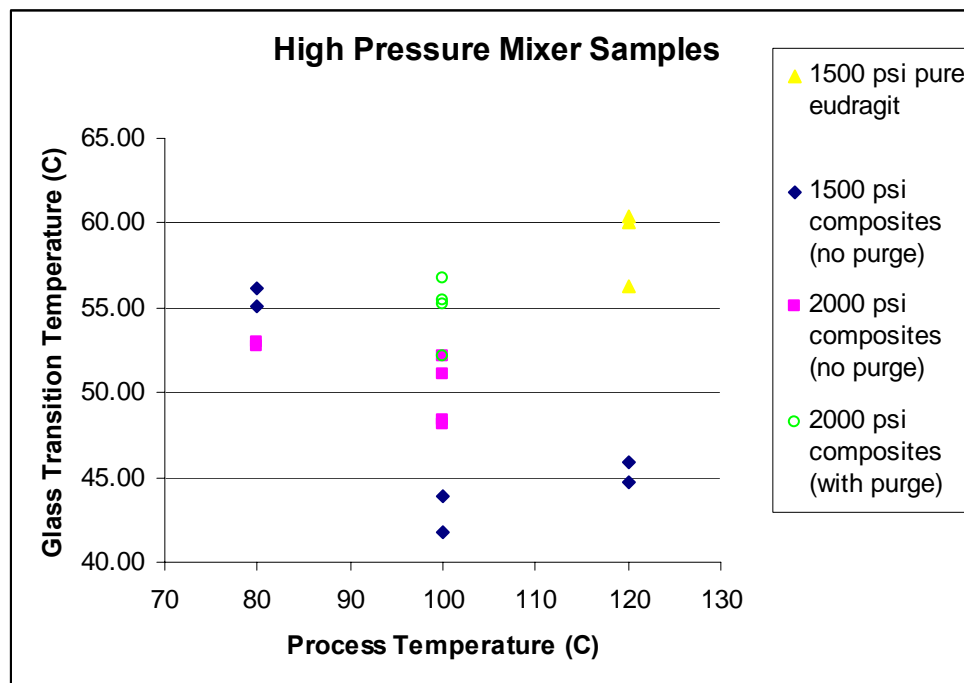


Figure 12: Tg vs. Process Temperature for HPM samples

High-pressure DSC scans were attempted for the amorphous drug-polymer dispersions formed at 100°C and 2000psi. However, because the starting temperature of these analyses was 25°C, and the baseline was very noisy at this temperature range, it was difficult to interpret any features of the plot. It should be noted that no T<sub>g</sub> transition was observed in the normal polymer range under pressurized CO<sub>2</sub> (200-250psi). It may be assumed that the polymer T<sub>g</sub> is depressed beyond its atmospheric range, but in order to gain any quantitative results, a cooling apparatus must be used in conjunction with the high pressure DSC to stabilize the baseline and allow a lower starting temperature.

### **3.3 Fourier Transform Infrared Spectroscopy Results**

Each composite sample, as well as the pure drug and polymer, were analyzed using FTIR spectroscopy. Because the absorbance values of the spectra are dictated by sample concentration, ideally each sample should have been made at identical concentrations. However, due to the accuracy of the scale in use, this was a difficult task. Figure 13 depicts the resulting IR spectra of the pure polymer, an organic solvent composite, and a high pressure mixer formulation (which was purged with CO<sub>2</sub> prior to heating to avoid drug degradation).

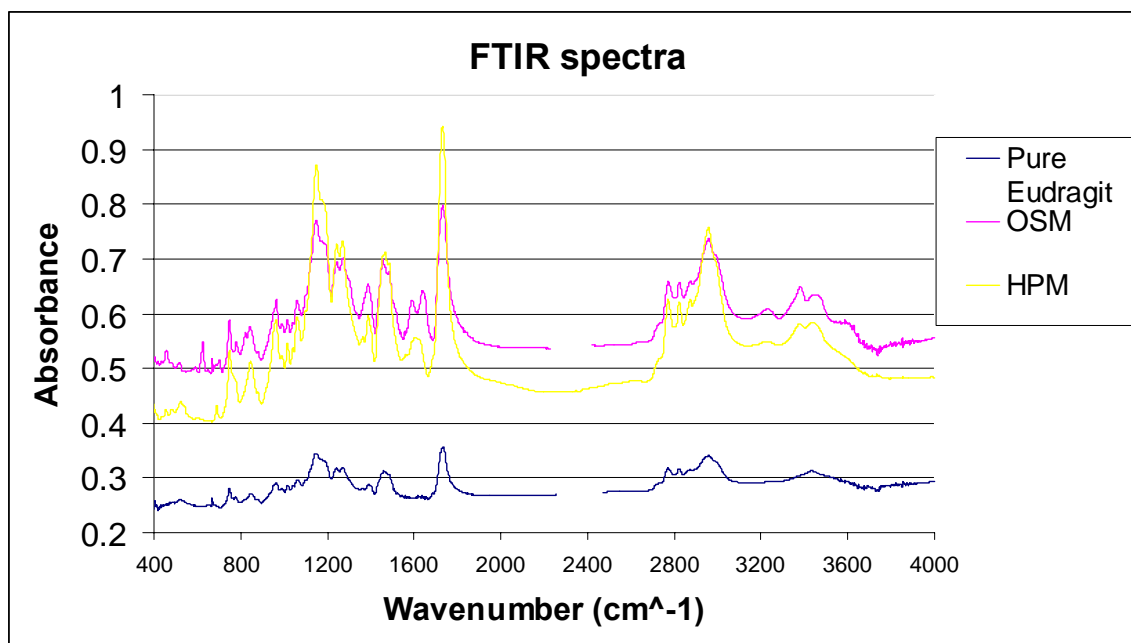


Figure 13: FTIR spectra of various samples

Although it is difficult to interpret the spectra at this scale due to variance in absorbance values, no distinctions can be made between the OSM and the HPM sample. In fact, only 4 features distinguish the 10 wt% composite from pure Eudragit. They consist of the following: (1) a doublet from 3200-3400  $\text{cm}^{-1}$ , indicating the presence of a primary amine, (2) a carbon-carbon double bond stretch near 1500  $\text{cm}^{-1}$ , (3) C-O-H in-plane bending around 1430  $\text{cm}^{-1}$ , and (4) a C-O-H out of plane bending around 930  $\text{cm}^{-1}$ .

The remainder of drug features, as well as any drug-polymer interaction, remains hidden in the strong Eudragit signal. No difference is observed for the drug in its amorphous state, and no drug degradation is evident from the IR spectra alone. In order for the FTIR technique to be an effective analysis method in determining drug degradation and drug-polymer interaction, a higher concentration of drug must be used.

#### IV. CONCLUSIONS

A method for producing pharmaceutical/polymer composites using a supercritical carbon dioxide-assisted high-pressure mixing process has been investigated. This batch operation has helped to determine the suitability of model materials for extrusion processes, while conserving costly pharmaceutical compounds. Porous foams were created using the high-pressure mixing process. Qualitatively, the advantages of the downstream processing of these foams relative to the organic solvent method products are obvious. Milling and grinding of the foam product greatly reduces thermal and mechanical stresses on the composite, thus minimizing product degradation during downstream processing.

Additionally, the plasticization effect of 4-aminosalicylic acid on Eudragit E100 has been confirmed. The glass transition temperature depression has been measured using differential scanning calorimetry. At 2000 psi, amorphous drug dispersions have been formed via the high-pressure mixing method, without any residual solvent. DSC results confirm that the drug is present in its crystalline form in the organic solvent method composites. Furthermore, a noisy drug melting peak indicates that residual solvent may be present in the organic solvent method processes. Amorphous drug dispersions should result in enhanced dissolution properties, and this increased dissolution rate represents another advantage of the foam product relative to the organic solvent method composite. However, the extended residence time in the high-pressure mixer results in significant drug degradation at lower temperatures than previous research has indicated for extrusion processes. Nevertheless, supercritical carbon dioxide-assisted

extrusion seems to be a promising technique for the processing of thermally-labile drug compounds in biodegradable polymers with low glass transition temperatures.

## **V. RECOMMENDATIONS**

### **5.1 Experimental Considerations**

For the organic solvent method composites, residual solvent remains a concern. Because the vacuum oven did not sufficiently remove the employed solvent, additional measures should be utilized. Perhaps a gas-solid fluidization column can be used to minimize residual solvent, by increasing the surface area of the product exposed to evaporation operations.

The advantages of purging the high-pressure mixer system with carbon dioxide prior to heating have been confirmed. This purging step helps to minimize drug degradation for the thermally-labile drug compound by preventing oxidation during the heating step. The effect of residence time in the mixer on composition properties should also be investigated, to more accurately simulate extrusion.

Additional analysis techniques should be employed to further confirm the conclusions drawn from this research. Composites should be made at increased drug concentrations, so that Fourier-transform infrared spectroscopy analyses can be used to examine drug-polymer interactions. Furthermore, high-pressure liquid chromatography techniques should be employed to quantitatively determine drug degradation, and examine the byproduct formation resulting from drug degradation.

### **5.2 Recommendations for Extrusion**

High-pressure differential scanning calorimetry analyses should be conducted on the experimental materials. Because of the low glass transition temperature of Eudragit E100, a cooling vessel should be attached to the HPDSC vessel for accuracy. By



determining the effect of high-pressure carbon dioxide on the glass transition temperature depression of the composite, minimal operating temperature for extrusion can be quantified. The extruder should then be operated at these temperatures to minimize degradation of the thermally-labile compound. Adequate control of residence time in the extruder should be confirmed, to ensure a consistent product and further control degradation.

Because the experimental materials were each susceptible to oxidation, the drug should be kept in a desiccator and purged with an inert gas before processing. Furthermore, an Aldrich® Atmosbag may be employed to minimize the atmospheric effects on the polymer prior to extrusion.

Separate powder and pellet feeders should be calibrated and used to feed the experimental materials into the hopper of the extruder. This feeding technique should result in a more consistent product composition than the product resulting from hand-mixing the drug and polymer prior to input into the hopper. If possible, the thermally-labile drug compound should be injected into the extruder after the addition of carbon dioxide to the polymeric carrier, to minimize the processing temperatures of the drug. Perhaps a tandem extrusion setup could be employed.

The composites resulting from extrusion should be compared to those produced by the high-pressure mixing method, to confirm the accuracy of the batch technique in simulating continuous extruder conditions.

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